Growth in utero and cognitive function in adult life: follow up study of people born between 1920 and 1943

Christopher N Martyn, Catharine R Gale, Avan Aihie Sayer, Caroline Fall

Abstract

Objectives—To examine the relation between fetal growth and cognitive function in adult life.

Design—A follow up study of men and women whose birth weights and other measurements of body size had been recorded at birth.

Setting—Hertfordshire, Preston, and Sheffield.

Subjects—1576 men and women born in Hertfordshire, Sheffield, or Preston between 1920 and 1943.

Main outcome measures—Intelligence quotient as measured by the AH4 test and amount of decline in cognitive function with age as estimated by the difference between score on the Mill Hill vocabulary test and score on the AH4 test.

Results—Score on the intelligence test was higher in people who had a large biparietal head diameter at birth, but it was not related to any other measure of body size or proportions. No association was found between decline in cognitive function and any measure of size or proportions at birth.

Conclusion—Impaired fetal growth was not associated with poorer cognitive performance in adult life. Adaptations made by the fetus in response to conditions that retard its growth seem to be largely successful in maintaining brain development.

Introduction

There is considerable evidence that malnutrition in early life can have an adverse effect on the developing brain.[1][2] During various critical periods in the development of the central nervous system, malnutrition has been shown to affect the morphology, physiology, and neurochemistry of the brain, and this may have important implications for future cognitive function.[3-5] Undernutrition during proliferative growth of the brain, for example, retards the rate of cell division and causes a permanent reduction in numbers of brain cells.[6] Animal studies suggest that such nutritional privation during fetal life affects later performance on tests of learning.[7] In humans, low birth weight and proportionate smallness at birth, both of which may result from undernutrition in utero, have been associated with poorer performance on tests of cognitive function in early childhood.[8-10] There have been few studies, however, on whether poor fetal growth has a lasting effect on adult cognitive performance.

In several community surveys of older people, cognitive function has been assessed by using the AH4 intelligence quotient (IQ) test and the Mill Hill vocabulary test.[11] Studies have shown that cognitive skills do not all deteriorate at the same rate.[12][13] The AH4 test provides a measure of fluid intelligence, which tends to decline with advancing age, while score on the Mill Hill vocabulary test gives an estimate of crystallised intelligence, which may be retained unimpaired until very late in life.[14] By measuring the discrepancy between scores on the two tests an indication of the amount of decline in cognitive ability can be obtained.[15] We studied the cognitive performance of older men and women who had been measured in unusual detail at birth. We investigated whether intrauterine growth was related to adult intelligence. Because we thought it possible that the rate of cognitive decline with age might be influenced by growth in utero, we also investigated whether birth measurements were associated with the discrepancy between score on the Mill Hill vocabulary test and score on the AH4 IQ test.

Subjects and methods

From 1911 onwards each child born in Hertfordshire was seen immediately after birth by a health visitor and its birth weight was recorded in centrally held registers. In Preston and Sheffield a standardised record was kept for each woman admitted to the labour wards at Sharoe Green Hospital and Jessop Hospital for Women, respectively. These records included details of the baby's birth weight, length from crown to heel, and measurements of abdominal circumference, head circumference, biparietal diameter, and occipitofrontal diameter. The NHS central register was used to trace singleton infants born to married mothers in Hertfordshire, Preston, and Sheffield. Those who were still living in the area of their birth were invited to take part in various studies into the processes by which the environment in early life influences adult disease.[16][17]

In this analysis we used five datasets comprising men and women who still lived in the area in which they were born. Subjects were invited to participate and were interviewed if they agreed. They were then invited to undergo psychometric testing. Table 1 gives details of the participants.

Subjects took part 1 of the AH4 IQ test, which provides a measure of logical, verbal, and numerical reasoning, and the Mill Hill vocabulary test. To obtain an estimate of the amount of decline in cognitive function, we standardised the scores on the two tests using Z scores and calculated the difference between them.[15]

We analysed all the datasets together, with multiple linear regression and tabulation of means to examine the relation between measurements of body size at birth, score on the AH4 intelligence test, and amount of change in cognitive function. Birth weight, length, ponderal index, and head circumference were divided into

MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD
Christopher N Martyn, *clinical scientist*
Catharine R Gale, *research student*
Avan Aihie Sayer, *Wellcome research fellow*
Caroline Fall, *clinical scientist*

Correspondence to:
Dr Martyn.

Table 1—*Details of participants and response rates*

Dataset	Sex	Birth place	Years	No invited to participate	No (%) interviewed	No (%) who took test
1	Women	East Hertfordshire	1920-30	565	388 (69)	295 (76)
2	Men and women	North Hertfordshire	1920-30	1428	824 (58)	694 (84)
3	Men and women	Preston	1935-43	393	266 (68)	107 (40)
4	Men and women	Sheffield	1939-40	419	337 (80)	227 (67)
5	Men and women	Sheffield	1922-6	513	322 (63)	253 (79)

Table 2—*Mean birth measurements, age, and score on psychometric tests. All figures are means (SD)*

Detail	All areas (n = 1576)	Herts 1 (n = 295)	Herts 2 (n = 694)	Preston (n = 107)	Sheffield 1 (n = 227)	Sheffield 2 (n = 253)
Birth measurement*:						
Birth weight (oz)	119.3 (18.5)	121.3 (19.2)	121.9 (17.8)	109.5 (18.6)	114.6 (17.8)	117.8 (18.3)
Length (in)	20.1 (1.1)	—	—	20.2 (1.1)	19.9 (1.0)	20.2 (1.1)
Ponderal index (oz/in^3)	14.2 (1.9)	—	—	13.2 (1.6)	14.5 (1.7)	14.3 (2.0)
Head circumference (in)	13.6 (0.7)	—	—	13.6 (0.8)	13.5 (0.7)	13.6 (0.7)
Occipitofrontal diameter (in)	4.5 (0.4)	—	—	4.4 (0.3)	4.5 (0.5)	4.4 (0.3)
Biparietal diameter (in)	3.6 (0.4)	—	—	3.5 (0.2)	3.7 (0.5)	3.5 (0.3)
Abdominal circumference (in)	12.3 (1.1)	—	—	—	12.4 (1.1)	12.2 (1.1)
Age (years)	60.9 (2.1)	63.6 (3.0)	67.1 (3.3)	53.3 (2.3)	52.1 (0.6)	68.6 (1.4)
AH4 score	22.5 (9.2)	21.2 (10.2)	22.1 (9.2)	25.4 (8.2)	24.8 (8.3)	21.6 (9.1)
Mill Hill score	18.0 (4.7)	17.0 (4.8)	18.0 (4.8)	19.1 (4.0)	18.7 (4.2)	18.2 (5.0)
Decline in cognitive function	0.03 (0.8)	0.04 (0.8)	0.04 (0.8)	−0.04 (0.9)	−0.01 (0.9)	0.04 (0.2)

*All measurements are given as originally recorded; 1 oz=28 g, 1 inch=2.5 cm.

groups in the same way as in previous studies of these subjects.[18-20] Categories of occipitofrontal diameter, biparietal diameter, head circumference to length ratio, and head circumference to abdominal circumference ratio were chosen by grouping into thirds of the distributions. We have shown the results as mean score on the AH4 test and mean amount of cognitive loss within each group of birth measurements. All values given for significance were calculated by regression with birth measurements used as continuous and not categorical variables. Mean score on the AH4 intelligence test was higher in those whose fathers were in non-manual occupations at the time of their birth and in younger subjects. Mean AH4 score also varied between the datasets. We adjusted for all these factors in regression. There were no significant differences between the sexes in either score on the AH4 test or change in cognitive function. When we analysed the sexes separately the findings were similar, and the results are shown for men and women combined.

Results

Table 2 shows mean birth measurements, age, scores on the two psychometric tests, and decline in cognitive function in all subjects combined and in each dataset separately. Mean score on the AH4 intelligence test was higher in the Preston and first Sheffield groups, in which the average age of subjects was younger. These two groups also showed less evidence of decline in cognitive function, as measured by the absolute difference between standardised scores on the Mill Hill vocabulary test and the AH4 test.

Mean score on the AH4 test was higher with increasing birth weight, but this trend was not significant (table 3). We found no relation between AH4 score and either length, head circumference, or occipitofrontal diameter at birth. Body proportions at birth, whether assessed by ponderal index, head circumference to length ratio, or head circumference to abdominal circumference ratio, were not related to AH4 score. On average, subjects who had a large biparietal diameter at birth had a higher AH4 score. After adjustment for age, social class at birth, and the individual datasets, the score on the AH4 test rose by 3.7 for each inch (2.5 cm) increase in biparietal diameter. We repeated all these analyses, excluding 82 subjects who had been born before 38 weeks of completed gestation. The relation between AH4 score and biparietal diameter persisted, but there were no associations with any other measure of body size or proportions.

We found no relation between decline in cognitive function, as estimated by the discrepancy between standardised scores on the two tests, and proportions at birth as assessed by head circumference to length ratio or head circumference to abdominal circumference ratio, nor was cognitive function related to any measure of head size (table 3). Neither birth weight nor length were associated with decline in cognitive function. We obtained similar results when we excluded subjects born before 38 completed weeks of gestation.

Table 3—*Mean score on the AH4 test and decline in cognitive function according to birth measurements*

Birth measurement*	No†	Mean AH4 score	P value‡	Mean decline in cognitive function	P value‡
Birth weight (lb):					
≤5.5	74	20.8		0.02	
5.6 - 6.5	266	21.8		0.06	
6.6 - 7.5	543	22.6		0.05	
>7.5	693	23.0	0.17	0.003	0.42
Length (in):					
<20	168	23.1		−0.06	
20	184	24.4		0.14	
>20	200	23.7	0.34	−0.07	0.98
Ponderal index (oz/in^3):					
≤13.2	166	22.9		−0.05	
13.3 - 14.3	136	23.3		0.01	
14.4 - 15.4	129	25.5		−0.01	
>15.4	121	23.5	0.43	0.09	0.09
Head circumference (in):					
≤13	163	23.1		−0.002	
13.1 - 13.8	177	23.6		−0.002	
>13.8	237	23.8	0.87	0.03	0.47
Occipitofrontal diameter (in):					
≤4.3	248	23.1		0.02	
4.4 - 4.5	183	24.0		0.03	
>4.5	149	23.6	0.48	−0.02	0.89
Biparietal diameter (in):					
≤3.5	219	23.0		0.05	
3.6 - 3.7	122	21.5		0.03	
>3.7	240	25.1	0.008	−0.03	0.85
Ratio of head circumference to length:					
≤0.66	176	24.1		−0.05	
0.67 - 0.69	180	23.5		0.06	
>0.69	189	23.7	0.28	0.1	0.31
Ratio of head to abdominal circumference:					
≤1.08	154	23.7		0.05	
1.09 - 1.13	134	23.8		−0.04	
>1.13	145	22.8	0.81	0.05	0.74

**All measurements are given as originally recorded; 1 oz=28 g, 1 inch=2.5 cm, 1 lb=453 g.
†Because of missing values for some birth measurements, numbers do not always add up to 1576.
‡Calculated by using all variables as continuous and adjusting for age, social class at birth, and individual dataset.

Discussion

In these data there were few associations between fetal growth and adult cognitive function. No relation was found between any measure of body size or proportions at birth and adult intelligence, with the exception of biparietal diameter. People with a large biparietal diameter at birth tended to gain higher scores on the

AH4 IQ test. No associations were found between decline in cognitive function related to age and either size or proportions at birth.

Our results are based on 1576 subjects who took the two psychometric tests. This is 47% of those originally invited to participate. Furthermore, the participants are unrepresentative of all people born in Hertfordshire, Sheffield, or Preston because they have continued to live in the area of their birth. All comparisons, however, have been made within the study sample. Unless the relations between birth measurements and cognitive function in adult life differ in non-responders or in people who have died or moved away, no bias will have been introduced.

Measurements of head circumference correlate closely with brain size at birth.[21] A small head circumference at one year has been associated with a lower score on intelligence tests in early childhood.[22] We found a significant association between biparietal diameter at birth and score on the AH4 IQ test in adult life, but this is hard to interpret in the absence of any association with other measurements of head size; it may be due to chance.

GROWTH RETARDATION IN GESTATION

Babies who have been exposed to chronic nutritional deprivation from the early stages of pregnancy may be proportionately small at birth, showing signs of growth retardation in all dimensions including head size.[23] Such babies are more prone to neurodevelopmental impairment. A follow up study of small for dates babies found that those who had experienced an early onset of failure of growth in utero had a lower score on tests of cognitive development at the age of 4 years.[24] Several studies have reported that babies who are proportionately small at birth, with growth retardation in both weight and length, show signs of impaired intellectual development in the first years of life.[8] [10] In contrast, when growth retardation occurs in mid or late gestation, head circumference and brain growth tend to be spared.[25] One mechanism for this involves cardiovascular adaptations that maintain blood flow to the brain at the expense of the trunk.[26] Babies who have experienced this sort of growth retardation may be identified by a raised ratio of head circumference to abdominal circumference.[27] Follow up studies of babies with growth failure in the later stages of pregnancy found no evidence of impaired intellectual development in early childhood.[10] [24] Babies who were exposed to the Dutch famine of 1944-5 during the third trimester of pregnancy were found to be growth retarded in weight and to a lesser extent in length and head circumference.[28] But when men born during this period were given a series of psychometric tests, no association was found between mental performance and prenatal exposure to famine.[29]

We examined the relation between mental performance and body proportions at birth but found no significant associations between AH4 score and either ponderal index, ratio of head circumference to length, or ratio of head circumference to abdominal circumference. AH4 score was higher with increasing birth weight, but this trend was not significant. The fact that we found no relation between growth in utero and cognitive performance may be related to the age of our subjects. They were born during a period when the survival chances of infants with a low birth weight or growth retardation were much smaller than today, and there may have been too few such babies among our subjects to detect any difference in cognitive function. An alternative explanation for our findings is that most of the growth retardation in our subjects occurred in mid or late gestation, when fetal redistribution of blood circulation allows preferential flow to the brain. Poor growth in fetal life, however, is only one of several potential factors which may inhibit brain development.

Key messages

- Animal experiments show that undernutrition during the period of proliferative growth of the fetal brain affects later performance on tests of learning

- In humans, low birth weight and proportionate smallness at birth have been associated with poorer cognitive function in early childhood, but there have been few studies on whether this association persists into adult life

- There was no relation between body size or proportions at birth and either intelligence or cognitive decline related to age in over 1500 people aged between 48 and 74 years whose birth measurements had been recorded

- Fetal growth seems to be less important than genetic factors and environmental influences in postnatal life in determining adult cognitive performance

- Adaptations made by the fetus in response to conditions that retard its growth may be largely successful in maintaining brain development

Parent-child relationships, the quality and amount of intellectual stimulation, and the socioeconomic environment into which the baby is born are all likely to operate synergistically to influence cognitive development.[30] Undernutrition in infancy and early childhood has been associated with poor mental function, though only in the presence of a lack of social and intellectual stimulation.[31] By the time the baby reaches adulthood, environmental factors in postnatal life may overshadow any effect of intrauterine experience on cognitive performance.

Many of the causes of cognitive decline in later life are still unclear. There are clear individual differences in the rates at which cognitive function changes with age, and only some of this variation can be explained by the presence of pathologies known to impair mental performance.[32] We speculated that as poor fetal growth is linked to several diseases of old age,[16] [17] there might be an association between cognitive decline and size at birth, but we found no significant relations with any measure of size or body proportions at birth.

CONCLUSIONS

Previous studies have found relations between birth measurements and cardiovascular disease and its risk factors. These findings have been interpreted as indicating that undernutrition and other adverse influences during critical periods in utero may permanently programme the body's structure, physiology, and metabolism, leading to an increased risk of disease in later life. We examined the cognitive function of older men and women who had been measured in unusual detail at birth to investigate whether impaired fetal growth was associated with poorer mental performance in later life, but found no strong associations. The psychometric tests used in this study do not provide a comprehensive test of cognitive abilities so there may be areas of mental function that are affected by poor growth in utero. None the less, our findings suggest that fetal growth is less important than genetic factors and environmental influences in postnatal life in determining adult cognitive performance. Adaptations made by the fetus in response to conditions that retard its growth seem to be largely successful in maintaining its brain development.

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Perioperative myocardial infarction in peripheral vascular surgery

N Mamode, R N Scott, S C McLaughlin, A McLelland, J G Pollock

The commonest major complication in patients undergoing peripheral vascular surgery is perioperative myocardial infarction.[1] No study in Britain has prospectively assessed this risk, but a recent retrospective study found an incidence of 6.3% in patients undergoing aortic surgery.[2] We report the incidence of perioperative myocardial infarction in our unit, which is a regional centre for peripheral vascular surgery.

Patients, methods, and results

We studied consecutive patients undergoing peripheral vascular surgery after excluding those who were undergoing surgery for trauma, venous surgery, and minor procedures. Patients thought to be at high risk of perioperative myocardial infarction were referred to a cardiologist for further preoperative assessment. Concentrations of creatinine kinase MB isoenzymes were measured (by Imx STAT) for the first three days after surgery, and electrocardiograms were recorded on admission, on discharge from hospital, and at doctors' discretion. Because the concentration of creatinine kinase MB isoenzyme may be raised by skeletal muscle ischaemia, myocardial infarction was diagnosed only when a raised total creatinine kinase concentration was associated with an MB subunit concentration of >10 ng/ml and a ratio of MB subunit to total creatinine kinase of $\geq 5\%$. Cardiac death was defined as death unequivocally related to myocardial infarction, heart failure, or arrhythmia. The primary end points of our study were myocardial infarction or cardiac death within 30 days of surgery. We performed statistical analysis with the χ^2 test or, when appropriate, Fisher's exact test.

The 191 patients included in our study (128 men, median age 65, and 63 women, median age 70) underwent 204 operations, of which 100 were elective procedures, 70 were urgent (requiring surgery within the same hospital admission), and 34 were emergency (requiring surgery within 24 hours). Ninety one of the operations were carried out for critical ischaemia, 32 were aortic procedures, and 120 patients (of the 182 in whom data were available) had preoperative evidence of ischaemic heart disease.

The overall incidence of perioperative myocardial infarction and cardiac death was 7.3%—6% for those undergoing elective or urgent procedures and 12% for those undergoing emergency surgery. Table 1 gives details of the six myocardial infarctions and eight cardiac deaths that occurred. Four of the non-fatal infarctions were clinically silent. Two patients had surgery performed under regional anaesthesia (amputation and brachial embolectomy), while the rest had a general anaesthetic. Three patients were submitted to necropsy, which showed subendocardial infarction in two patients and transmural infarction (probably preceding surgery) in the other. The factors associated with perioperative myocardial infarction were age over 70 ($\chi^2 = 4.642$, P=0.03), sex ($\chi^2 = 3.989$, P=.05), perioperative shock (Fisher's exact test $\chi^2 = 6.949$, P=0.05), and angina (Fisher's exact test $\chi^2 = 7.317$, P=0.008).

Peripheral Vascular Unit, Glasgow Royal Infirmary, Glasgow G31 2ER
N Mamode, registrar
R N Scott, senior registrar
J G Pollock, consultant vascular surgeon

Department of Medical Cardiology, Glasgow Royal Infirmary
S C McLaughlin, research assistant

Department of Biochemistry, Glasgow Royal Infirmary
A McLelland, top grade biochemist

Correspondence to:
Mr Mamode.

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